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(54) Title: METERED DOSE INHALER FOR SALMETEROL

(57) Abstract

A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising salmeterol, or a physiologically acceptable salt thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

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METERED DOSE INHALER FOR SALMETEROL**BACKGROUND OF THE INVENTION**

5 Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such aerosol drug formulations involves making a suspension formulation of the drug as a finely divided powder in a liquefied gas known as a propellant. The suspension is stored in a sealed container capable of
10 withstanding the pressure required to maintain the propellant as a liquid. The suspension is dispersed by activation of a dose metering valve affixed to the container.

15 A metering valve may be designed to consistently release a fixed, predetermined mass of the drug formulation upon each activation. As the suspension is forced from the container through the dose metering valve by the high vapor pressure of the propellant, the propellant rapidly vaporizes leaving a fast moving cloud of very fine particles of the drug formulation. This cloud of particles is directed into the nose or mouth of the patient by a channelling device such as a cylinder or open-ended cone. Concurrently with the activation of the aerosol dose metering valve, the patient inhales the drug particles into the lungs or nasal cavity. Systems of dispensing drugs in this way are known as "metered dose inhalers" (MDI's). See Peter Byron, *Respiratory Drug Delivery*, CRC Press, Boca Raton, FL (1990) for a general background on this form of therapy.

25 Patients often rely on medication delivered by MDI's for rapid treatment of respiratory disorders which are debilitating and in some cases, even life threatening. Therefore, it is essential that the prescribed dose of aerosol medication delivered to the patient consistently meet the specifications claimed by
30 the manufacturer and comply with the requirements of the FDA and other regulatory authorities. That is, every dose in the can must be the same within close tolerances.

Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the can, valves, and caps, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of drug upon each activation of the MDI. The problem is particularly acute with hydrofluoroalkane (also known as simply "fluorocarbon")

5 propellant systems, e.g., P134a and P227, under development in recent years to replace chlorofluorocarbons such as P11, P114 and P12.

We have found that coating the interior can surfaces of MDI's with a fluorocarbon polymer significantly reduces or essentially eliminates the problem of adhesion or 10 deposition of salmeterol on the can walls and thus ensures consistent delivery of medication in aerosol from the MDI.

SUMMARY OF THE INVENTION

15 A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising salmeterol, or a physiologically acceptable salt thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically 20 active agents or one or more excipients.

DETAILED DESCRIPTION OF THE INVENTION

The term "metered dose inhaler" or "MDI" means a unit comprising a can, a 25 crimped cap covering the mouth of the can, and a drug metering valve situated in the cap, while the term "MDI system" also includes a suitable channelling device. The terms "MDI can" means the container without the cap and valve. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an 30 MDI upon each activation. The channelling device may comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts

of a typical MDI is illustrated in US Patent 5,261,538 incorporated herein by reference.

The term "fluorocarbon polymers" means a polymer in which one or more of the 5 hydrogen atoms of the hydrocarbon chain have been replaced by fluorine atoms. Thus, "fluorocarbon polymers" include perfluorocarbon, hydrofluorocarbon, chlorofluorocarbon, hydro-chlorofluorocarbon polymers or other halogen substituted derivatives thereof. The "fluorocarbon polymers" may be branched, homo-polymers or co-polymers.

10 U.S. Patent No.4,992,474, incorporated herein by reference, teaches a bronchodilating compound particularly useful in the treatment of asthma and other respiratory diseases know by the chemical name 4-hydroxy- α ¹-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol and the generic name 15 "salmeterol". Salmeterol as the free base and as acid addition salts (particularly as the 1-hydroxy-2-naphthalenecarboxylic acid salt also known as hydroxynaphthoate or xinafoate salt), especially in aerosol form, has been accepted by the medical community as a useful treatment of asthma and is marketed under the trademark "Serevent"

20 The term "drug formulation" means salmeterol or a physiologically acceptable salt thereof (particularly the hydroxynaphthoate salt) optionally in combination with one or more other pharmacologically active agents such as antiinflammatory agents, analgesic agents or other respiratory drugs and optionally containing one or more 25 excipients. The term "excipients" as used herein mean chemical agents having little or no pharmacological activity (for the quantities used) but which enhance the drug formulation or the performance of the MDI system. For example, excipients include but are not limited to surfactants, preservatives, flavorings, antioxidants, antiaggregating agents, and cosolvents, e.g., ethanol and diethyl ether.

30 Salmeterol or salt thereof may be used in the form of its R-isomer.

Suitable surfactants are generally known in the art, for example, those surfactants disclosed in European Patent Application No. 0327777. The amount of surfactant

employed is desirable in the range of 0.0001% to 50% weight to weight ratio relative to the drug, in particular, 0.05 to 5% weight to weight ratio. A particularly useful surfactant is 1,2-di[7-(F-hexyl) hexanoyl]- glycero-3-phospho-N,N,N-trimethylethanolamine also known as 3, 5, 9-trioxa-4-phosphadocosan-1-aminium,
5 17, 17, 18, 18, 19, 19, 20, 20, 21, 21, 22, 22, 22-tridecafluoro-7-[(8, 8, 9, 9, 10, 10,
11, 11, 12, 12, 13, 13, 13-tridecafluoro-1-oxotridecyl)oxy]-4-hydroxy-N, N, N-
trimethyl-10-oxo-, inner salt, 4-oxide.

10 A polar cosolvent such as C_{2-6} aliphatic alcohols and polyols e.g. ethanol, isopropanol and propylene glycol, preferably ethanol may be included in the drug formulation in the desired amount, either as the only excipient or in addition to other excipients such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar cosolvent e.g. ethanol, preferably 0.1 to 5% w/w e.g. about 0.1 to 1% w/w.

15 It will be appreciated by those skilled in the art that the drug formulation for use in the invention may, if desired, contain salmeterol or a salt thereof in combination with one or more other pharmacologically active agents. Such medicaments may be selected from any suitable drug useful in inhalation therapy. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. 20 beclomethasone (e.g. the dipropionate), flunisolide, budesonide, tipredane or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. salbutamol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5-25 dichloro- α -[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and
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therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the 5 activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred drug formulations contain salmeterol or a physiologically acceptable salt thereof in combination with an anti-inflammatory steroid such as 10 fluticasone propionate, beclomethasone dipropionate or physiologically acceptable solvates thereof.

A particularly preferred drug combination is salmeterol xinafoate and fluticasone propionate.

15 "Propellants" used herein mean pharmacologically inert liquids with boiling points from about room temperature (25°C) to about -25°C which singly or in combination exert a high vapor pressure at room temperature. Upon activation of the MDI system, the high vapor pressure of the propellant in the MDI forces a metered 20 amount of drug formulation out through the metering valve then the propellant very rapidly vaporizes dispersing the drug particles. The propellants used in the present invention are low boiling fluorocarbons; in particular, 1,1,1,2-tetrafluoroethane also known as "propellant 134a" or "P 134a" and 1,1,1,2,3,3,3-heptafluoro-n-propane also known as "propellant 227" or "P 227".

25 Drug formulations for use in the invention may be free or substantially free of formulation excipients e.g. surfactants and cosolvents etc. Such drug formulations are advantageous since they may be substantially taste and odour free, less irritant and less toxic than excipient-containing formulations. Thus, a 30 preferred drug formulation consists essentially of salmeterol or a physiologically acceptable salt thereof, e.g. the xinafoate salt, optionally in combination with one or more other pharmacologically active agents particularly fluticasone propionate (or a physiologically acceptable solvate thereof), and a fluorocarbon propellant.

Preferred propellants are 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

Further drug formulations for use in the invention may be free or substantially free of surfactant. Thus, a further preferred drug formulation comprises or consists essentially of albuterol (or a physiologically acceptable salt thereof), optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 5% w/w based upon propellant of a polar cosolvent, which formulation is substantially free of surfactant. Preferred propellants are 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane.

Most often the MDI can and cap are made of aluminum or an alloy of aluminum, although other metals not affected by the drug formulation, such as stainless steel an alloy of copper, or tin plate, may be used. An MDI can may also be fabricated from glass or plastic. Preferably, however, the MDI cans employed in the present invention are made of aluminium or an alloy thereof. Advantageously, strengthened aluminium or aluminum alloy MDI cans may be employed. Such strengthened MDI cans are capable of withstanding particularly stressful coating and curing conditions, e.g. particularly high temperatures, which may be required for certain fluorocarbon polymers. Strengthened MDI cans which have a reduced tendency to malform under high temperatures include MDI cans comprising side walls and a base of increased thickness and MDI cans comprising a substantially ellipsoidal base (which increases the angle between the side walls and the base of the can), rather than the hemispherical base of standard MDI cans. MDI cans having an ellipsoidal base offer the further advantage of facilitating the coating process.

The drug metering valve consists of parts usually made of stainless steel, a pharmacologically inert and propellant resistant polymer, such as acetal, polyamide (e.g., Nylon[®]), polycarbonate, polyester, fluorocarbon polymer (e.g., Teflon[®]) or a combination of these materials. Additionally, seals and "O" rings of

various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

Fluorocarbon polymers for use in the invention include fluorocarbon polymers 5 which are made of multiples of one or more of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinylidenefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Fluorinated polymers which have a relatively high ratio of fluorine to carbon, such 10 as perfluorocarbon polymers e.g. PTFE, PFA, and FEP, are preferred.

The fluorinated polymer may be blended with non-fluorinated polymers such as polyamides, polyimides, polyethersulfones, polyphenylene sulfides and amine-formaldehyde thermosetting resins. These added polymers improve adhesion of 15 the polymer coating to the can walls. Preferred polymer blends are PTFE/FEP/polyamideimide, PTFE/polyethersulphone (PES) and FEP-benzoguanamine.

Particularly preferred coatings are pure PFA, FEP and blends of PTFE and 20 polyethersulphone (PES).

Fluorocarbon polymers are marketed under trademarks such as Teflon®, Tefzel®, Halar®, Hostaflon®, Polyflon® and Neoflon®. Grades of polymer include FEP DuPont 856-200, PFA DuPont 857-200, PTFE-PES DuPont 3200-100, PTFE- 25 FEP-polyamideimide DuPont 856P23485, FEP powder DuPont 532, and PFA Hoechst 6900n. The coating thickness is in the range of about 1μm to about 1mm. Suitably the coating thickness is in the range of about 1μm to about 100μm, e.g. 1μm to 25μm. Coatings may be applied in one or more coats.

30 Preferably the fluorocarbon polymers for use in the invention are coated on to MDI cans made of metal, especially MDI cans made of aluminium or an alloy thereof.

The particle size of the particular (e.g., micronised) drug should be such as to permit inhalation of substantially all the drug into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and preferably in the range of 1-10 microns, e.g., 1-5 microns.

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The final aerosol formulation desirably contains 0.005-10% weight to weight ratio, in particular 0.005-5% weight to weight ratio, especially 0.01-1.0% weight to weight ratio, of drug relative to the total weight of the formulation.

10 A further aspect of the present invention is a metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispersing an inhalation drug formulation comprising salmeterol or a salt thereof and a fluorocarbon propellant optionally in combination with one or more other pharmacologically active agents and one or more excipients.

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20 A particular aspect of the present invention is an MDI having part or essentially all of its internal metallic surfaces coated with PFA or FEP, or blended fluoropolymer resin systems such as PTFE-PES with or without a primer coat of a polyamideimide or polyethersulfone for dispensing a drug formulation as defined hereinabove. Preferred drug formulations for use in this MDI consist essentially of salmeterol (or a salt thereof, e.g. the xinafoate salt), optionally in combination with one or more other pharmacologically active agents particularly fluticasone propionate or a physiologically acceptable solvate thereof and a fluorocarbon propellant, particularly 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane. Preferably the MDI can is made of aluminium or an alloy thereof.

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30 The MDI can may be coated by the means known in the art of metal coating. For example, a metal, such as aluminum or stainless steel, may be precoated as coil stock and cured before being stamped or drawn into the can shape. This method is well suited to high volume production for two reasons. First, the art of coating coil stock is well developed and several manufacturers can custom coat metal coil

stock to high standards of uniformity and in a wide range of thicknesses. Second, the precoated stock can be stamped or drawn at high speeds and precision by essentially the same methods used to draw or stamp uncoated stock.

- 5 Other techniques for obtaining coated cans is by electrostatic dry powdered coating or by spraying preformed MDI cans inside with formulations of the coating fluorinated polymer/polymer blend and then curing. The preformed MDI cans may also be dipped in the fluorocarbon polymer/polymer blend coating formulation and cured, thus becoming coated on the inside and out. The fluorocarbon
- 10 polymer/polymer blend formulation may also be poured inside the MDI cans then drained out leaving the insides with the polymer coat. Conveniently, for ease of manufacture, preformed MDI cans are spray-coated with the fluorinated polymer/polymer blend.
- 15 The fluorocarbon polymer/polymer blend may also be formed in situ at the can walls using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer film may be blown inside the MDI cans to form bags. A variety of fluorocarbon polymers such as ETFE, FEP, and PTFE are available as film stock.
- 20 The appropriate curing temperature is dependent on the fluorocarbon polymer/polymer blend chosen for the coating and the coating method employed. However, for coil coating and spray coating temperatures in excess of the melting point of the polymer are typically required, for example, about 50°C above the melting point for up to about 20 minutes such as about 5 to 10 minutes e.g. about
- 25 8 minutes or as required. For the above named preferred and particularly preferred fluorocarbon polymer/polymer blends curing temperatures in the range of about 300°C to about 400°C, e.g. about 350°C to 380°C are suitable. For plasma polymerization typically temperatures in the range of about 20°C to about 100°C may be employed.
- 30 The MDI's taught herein may be prepared by methods of the art (e.g., see Byron, above and U.S. patent 5,345,980) substituting conventional cans for those coated with a fluorinated polymer/polymer blend. That is, salmeterol or a salt thereof and

other components of the formulation are filled into an aerosol can coated with a fluorinated polymer/polymer blend. The can is fitted with a cap assembly which is crimped in place. The suspension of the drug in the fluorocarbon propellant in liquid form may be introduced through the metering valve as taught in U.S.

5 5,345,980 incorporated herein by reference.

The MDI's with fluorocarbon polymer/polymer blend coated interiors taught herein may be used in medical practice in a similar manner as non-coated MDI's now in clinical use. However the MDI's taught herein are particularly useful for containing
10 and dispensing inhaled drug formulations with hydrofluoroalkane fluorocarbon propellants such as 134a with little, or essentially no, excipient and which tend to deposit or cling to the interior walls and parts of the MDI system. In certain cases it is advantageous to dispense an inhalation drug with essentially no excipient, e.g., where the patient may be allergic to an excipient or the drug reacts with an
15 excipient.

MDI's containing the formulations described hereinabove, MDI systems and the use of such MDI systems for the treatment of respiratory disorders e.g. asthma comprise further aspects of the present invention.

20 It will be apparent to those skilled in the art that modifications to the invention described herein can readily be made without departing from the spirit of the invention. Protection is sought for all the subject matter described herein including any such modifications.

25 The following non-limitative Examples serve to illustrate the invention.

EXAMPLES

30 Example 1

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) were spray-coated (Livingstone Coatings, Charlotte, NC) with primer (DuPont 851-204) and cured to

the vendor's standard procedure, then further spray-coated with either FEP or PFA (DuPont 856-200 and 857-200, respectively) and cured according to the vendor's standard procedure. The thickness of the coating is approximately 10 mm to 50 mm. These cans are then purged of air (see PCT application number

5 WO94/22722 (PCT/EP94/00921)), the valves crimped in place, and a suspension of about 4 mg salmeterol xinafoate (hydroxynaphthoate) in about 12 gm P134a is filled through the valve.

Example 2

10 Standard 0.46 mm thick aluminum sheet (United Aluminum) was spray-coated (DuPont, Wilmington, DE) with FEP (DuPont 856-200) and cured. This sheet was then deep-drawn into cans (Presspart Inc., Cary, NC). These cans were then purged of air, the valves crimped in place, and a suspension of about 2.5 mg

15 salmeterol xinafoate (hydroxynaphthoate) in about 7.5 gm P134A was filled through the valve.

Example 3

20 Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 6.1 mg of micronised salmeterol xinafoate in

25 about 12 g P134a is filled through the valve.

Example 4

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with

30 PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air the valves crimped in

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place, and a suspension of about 6.1 mg of micronised salmeterol xinafoate in about 12 g P134a is filled through the valve.

Example 5

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Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 6.1 mg of 10 micronised salmeterol xinafoate in about 12 g P134a is filled through the valve.

Example 6

Standard 0.46 mm thick aluminium sheet (United Aluminium) is spray coated with 15 FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and a suspension of about 6.1 mg of micronised salmeterol xinafoate in about 12 g P134a is filled through the valve.

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Example 7

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are 25 then purged of air, the valves crimped in place, and a suspension of about 6.1 mg of micronised salmeterol xinafoate in about 12 g respectively P134a is filled through the valve.

Example 8

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Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1 μm

and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 4.25 mg of micronised salmeterol xinafoate in about 8 g P134a is filled through the valve.

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Example 9

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1 μm 10 and approximately 20 μm . These cans are then purged of air the valves crimped in place, and a suspension of about 4.25 mg of micronised salmeterol xinafoate in about 8 g P134a is filled through the valve.

Example 10

15

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 4.25 mg of 20 micronised salmeterol xinafoate in about 8 g P134a is filled through the valve.

Example 11

Standard 0.46 mm thick aluminium sheet (United Aluminium) is spray coated with 25 FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and a suspension of about 4.25 mg of micronised salmeterol xinafoate in about 8 g P134a is filled through the valve.

30

Example 12

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the

coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 4.25 mg of micronised salmeterol xinafoate in about 8 g P134a is filled through the valve.

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Example 13

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's 10 standard procedure. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 6.4 mg micronised salmeterol xinafoate with about 8.8 mg, 22 mg or 44 mg micronised fluticasone propionate in about 12 g P134a is filled through the valve.

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Example 14

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's 20 standard procedure. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air the valves crimped in place, and a suspension of about 6.4 mg micronised salmeterol xinafoate with about 8.8 mg, 22 mg or 44 mg micronised fluticasone propionate in about 12 g P134a is filled through the valve.

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Example 15

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating 30 is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 6.4 mg micronised salmeterol xinafoate with about 8.8 mg, 22 mg or 44 mg micronised fluticasone propionate in about 12 g P134a is filled through the valve.

Example 16

Standard 0.46 mm thick aluminium sheet (United Aluminium) is spray coated with

5 FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and a suspension of about 6.4 mg micronised salmeterol xinafoate with about 8.8 mg, 22 mg or 44 mg micronised fluticasone propionate in about 12 g P134a is filled through the valve.

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Example 17

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the

15 coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 6.4 mg micronised salmeterol xinafoate with about 8.8 mg, 22 mg or 44 mg micronised fluticasone propionate in about 12 g P134a is filled through the valve.

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Example 18

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1 μm

25 and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 4 mg micronised salmeterol xinafoate with about 5.5 mg, 13.8 mg or 27.5 mg fluticasone propionate in about 8 g P134a is filled through the valve.

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Example 19

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's

standard procedure. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air the valves crimped in place, and a suspension of about 4 mg micronised salmeterol xinafoate with about 5.5 mg, 13.8 mg or 27.5 mg fluticasone propionate in about 8 g P134a is filled through the valve.

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Example 20

Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 4 mg micronised salmeterol xinafoate with about 5.5 mg, 13.8 mg or 27.5 mg fluticasone propionate in about 8 g P134a is filled through the valve.

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Example 21

Standard 0.46 mm thick aluminium sheet (United Aluminium) is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and a suspension of about 4 mg micronised salmeterol xinafoate with about 5.5 mg, 13.8 mg or 27.5 mg fluticasone propionate in about 8 g P134a is filled through the valve.

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Example 22

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Standard 12.5 ml MDI cans (Presspart Inc., Cary, NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1 μm and approximately 20 μm . These cans are then purged of air, the valves crimped in place, and a suspension of about 4 mg micronised salmeterol xinafoate with about 5.5 mg, 13.8 mg or 27.5 mg fluticasone propionate in about 8 g P134a is filled through the valve.

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Examples 23-28

Examples 3 to 7 are repeated except that a suspension of about 9.6 mg micronised salmeterol xinafoate in about 21.4 g P227 is filled through the valve.

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Examples 29-33

Examples 3 to 7 are repeated except that about 9.6 mg micronised salmeterol xinafoate in about 182 mg ethanol and about 18.2 g P134a is filled through the
10 valve.

Examples 34 - 64

Examples 3 to 33 are repeated except that modified 12.5 ml MDI cans (Presspart
15 Inc. Cary, NC) with an ellipsoid base are used.

Dose delivery from the MDIs tested under simulated use conditions is found to be constant, compared to control MDIs filled into uncoated cans which exhibit a significant decrease in dose delivered through use.

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We claim:

1. A metered dose Inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising salmeterol, or a physiologically acceptable salt thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.
- 5 10 2. An inhaler according to Claim 1 containing said drug formulation.
3. An inhaler according to Claim 2, wherein said drug formulation further comprises a surfactant.
- 15 20 4. An inhaler according to Claim 2 or Claim 3, wherein said drug formulation further comprises a polar cosolvent.
5. An inhaler according to Claim 2 wherein said drug formulation comprises 0.01 to 5% w/w based upon propellant of a polar cosolvent, which formulation is substantially free of surfactant.
- 25 6. An inhaler according to any one of Claims 2 to 5, wherein said drug formulation comprises salmeterol or a physiologically acceptable salt thereof in combination with an antiinflammatory steroid or an antiallergic.
7. An inhaler according to Claim 6, wherein said drug formulation comprises salmeterol xinafoate in combination with fluticasone propionate.
- 30 8. An inhaler according to Claim 2, wherein said drug formulation consists essentially of salmeterol or a physiologically acceptable salt thereof, optionally in combination with one or more other pharmacologically active agents, and a fluorocarbon propellant.

9. An inhaler according to Claim 8, wherein said drug formulation consists essentially of salmeterol or a physiologically acceptable salt thereof in combination with an antiinflammatory steroid or an antiallergic.
- 5 10. An inhaler according to Claim 9, wherein said drug formulation consists essentially of salmeterol or a physiologically acceptable solvate thereof in combination with fluticasone propionate or a physiologically acceptable solvate thereof.
- 10 11. An inhaler according to Claim 2, wherein said drug formulation consists of salmeterol or a physiologically acceptable salt thereof and a fluorocarbon propellant.
- 15 12. An inhaler according to any one of Claims 2 to 11 wherein the salmeterol is in the form of the xinafoate salt.
13. An inhaler according to any one of Claims 2 to 12, wherein the fluorocarbon propellant is 1,1,1,2- tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-
n-propane or mixtures thereof.
- 20 14. An inhaler according to Claim 13, wherein the fluorocarbon propellant is 1,1,1,2- tetrafluoroethane.
15. An inhaler according to any of Claims 1 to 14 comprising a can made of metal wherein part or all of the internal metallic surfaces are coated.
- 25 16. An inhaler according to Claim 15 wherein the metal is aluminium or an alloy thereof.
- 30 17. An inhaler according to any one of Claims 1 to 16 wherein said fluorocarbon polymer is a perfluorocarbon polymer.

18. An inhaler according to Claim 17 wherein said fluorocarbon polymer is selected from PTFE, PFA, FEP and mixtures thereof.
- 5 19. An inhaler according to any one of Claims 1 to 18, wherein said fluorocarbon polymer is in combination with a non-fluorocarbon polymer selected from polyamideimide and polyethersulphone.
- 10 20. An inhaler according to any one of Claims 1 to 19 comprising a substantially ellipsoidal base.
- 15 21. A metered dose inhaler system comprising a metered dose inhaler according to any one of Claim 1 to 20 fitted into suitable channelling device for oral or nasal inhalation of the drug formulation.
22. Use of a metered dose inhaler system according to Claim 21 for the treatment of respiratory disorders.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 96/05005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M15/00 B65D83/14 B05D5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M B65D B05D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 642 992 (CIBA-GEIGY AG) 15 March 1995	1,17,18
Y	see column 4, line 50 - column 5, line 6; claims 5-8	2-13,15, 16,19-22
Y	W0,A,93 11745 (GLAXO GROUP LTD.) 24 June 1993 see abstract see page 4, line 9 - page 5, line 9	2,4-13, 15,16
Y	W0,A,92 08446 (GLAXO GROUP LTD.) 29 May 1992 see page 3, last paragraph - page 4, paragraph 1	3
Y	EP,A,0 343 015 (SUMITOMO LTD.) 23 November 1989 see claims 1,10	19

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 465 741 (MITSUI TOATSU CHEMICALS ; TOKAI CORP (JP)) 15 January 1992 see claim 6 ---	20-22
A	US,A,5 176 132 (DROUGHT ET AL.) 5 January 1993 see column 3, paragraph 3 ---	1
A	WO,A,92 20391 (ABBOTT LABS) 26 November 1992 see abstract -----	20-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/05005

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-642992	15-03-95	AU-B-	7142994	09-03-95
		CA-A-	2130867	28-02-95
		JP-A-	7076380	20-03-95

WO-A-9311745	24-06-93	AT-T-	128350	15-10-95
		AU-B-	663906	26-10-95
		AU-B-	3085292	19-07-93
		CA-A-	2125665	24-06-93
		DE-D-	69205177	02-11-95
		DE-T-	69205177	21-03-96
		EP-A-	0616525	28-09-94
		ES-T-	2079210	01-01-96
		JP-T-	7501811	23-02-95
		NZ-A-	246046	21-12-95
		ZA-A-	9209618	09-08-93
		AP-A-	402	22-08-95
		AU-B-	663904	26-10-95
		AU-B-	3085092	19-07-93
		AU-B-	663905	26-10-95
		AU-B-	3085192	19-07-93
		BG-A-	98803	28-02-95
		CA-A-	2125666	24-06-93
		CA-A-	2125667	24-06-93
		CN-A-	1075078	11-08-93
		CN-A-	1075079	11-08-93
		CZ-A-	9401430	15-03-95
		WO-A-	9311743	24-06-93
		WO-A-	9311744	24-06-93
		EP-A-	0616523	28-09-94
		EP-A-	0616524	28-09-94
		HU-A-	67534	28-04-95
		JP-T-	7502033	02-03-95
		JP-T-	7502034	02-03-95
		NO-A-	942185	10-06-94
		NZ-A-	246044	26-01-96
		OA-A-	9926	15-09-94
		SK-A-	67494	08-03-95

WO-A-9208446	29-05-92	AT-T-	127013	15-09-95
		AU-B-	660952	13-07-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte	inal Application No
PCT/US 96/05005	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9208446		AU-B- 8877891		11-06-92
		CA-A- 2094726		10-05-92
		DE-D- 69112637		05-10-95
		DE-T- 69112637		08-02-96
		EP-A- 0556256		25-08-93
		ES-T- 2078551		16-12-95
		JP-T- 6501700		24-02-94
EP-A-343015	23-11-89	JP-A- 2089633		29-03-90
		US-A- 5009959		23-04-91
EP-A-0465741	15-01-92	US-A- 5083685		28-01-92
		AU-B- 614234		22-08-91
		AU-A- 5798690		22-08-91
US-A-5176132	05-01-93	US-A- 5482946		09-01-96
		US-A- 5341800		30-08-94
		AT-T- 111364		15-09-94
		CA-A- 2017883		30-11-90
		DE-D- 69012458		20-10-94
		DE-T- 69012458		09-03-95
		DE-T- 407028		17-03-94
		EP-A- 0407028		09-01-91
		ES-T- 2060040		16-11-94
		JP-A- 3018376		25-01-91
WO-A-9220391	26-11-92	AU-B- 663093		28-09-95
		AU-B- 2006592		30-12-92
		CA-A- 2107792		22-11-92
		EP-A- 0585379		09-03-94
		HU-A- 67175		28-02-95
		JP-T- 6507801		08-09-94
		NO-A- 934186		20-01-94
		PT-A- 100504		31-05-94

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